Continuous dynamic modeling

Input: components; interactions;
continuous states of components (e.g. concentrations)

Hypotheses: interaction network;
continuous transfer functions (e.g. mass-action-like, Hill function)
parameters- need to be estimated

Output: behavior of components in time

Validation: capture known behavior

Explore: study cases that are not accessible experimentally (e.g. perturbations)
change parameters, change assumptions

Parameter estimation

- Even the best model will not reproduce, explain or predict biological functionality it its parameter values are wrong.

- The goal of parameter estimation is to determine the parameter vector that minimizes the difference between experimental data and the model.
- The function to be minimized is usually the sum of the square differences between data and model.

- Parameter estimation is relatively straightforward for linear models, much more difficult for nonlinear ones (that is, the vast majority)

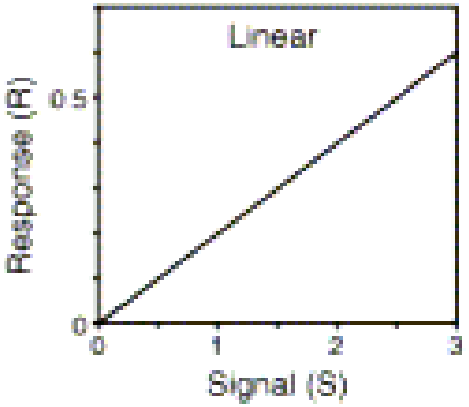
Continuous model of protein synthesis and degradation

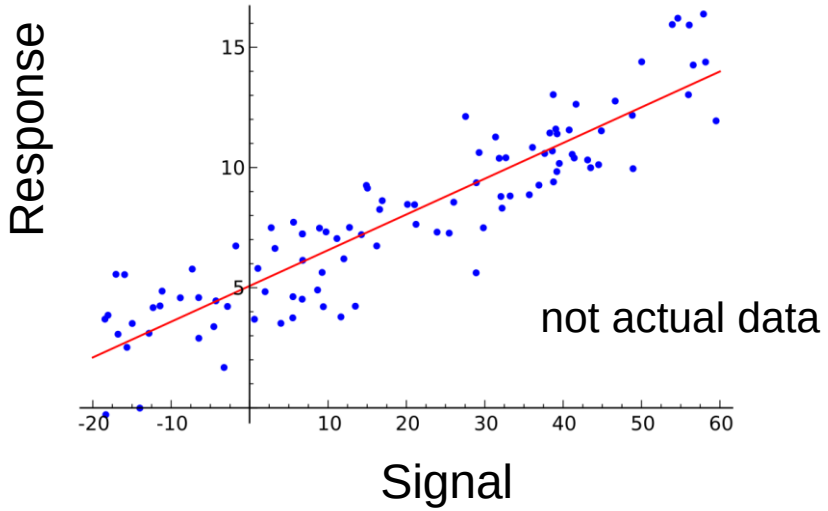
Protein synthesis: mRNA → protein

Protein degradation: protein →

$$\frac{dR}{dt} = k_1 S - k_2 R$$

Steady state: $R_{ss} = \frac{k_1 S}{k_2}$





For linear functions we can use linear regression on scatterplot from experimental data

The slope gives k_1/k_2

Continuous model of phosphotransfer

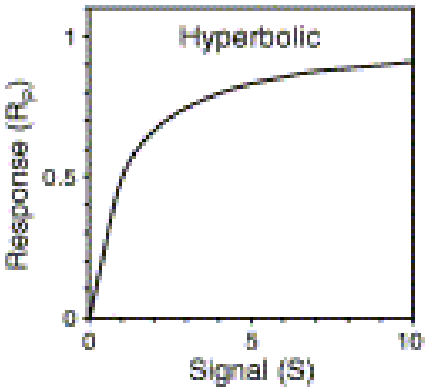
Phosphorylation: protein → phospho-protein

Dephosphorylation: phospho-protein → protein

The first reaction is catalyzed by a kinase, assume first –order kinetics

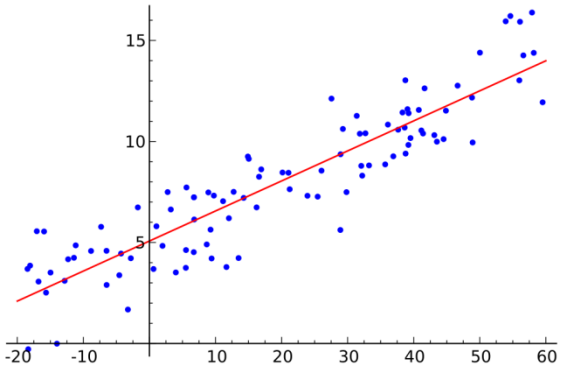
$$\frac{dR_P}{dt} = k_1 SR - k_2 R_P = -\frac{dR}{dt}$$

$$R_{P\,ss} = R_T \frac{S}{k_2/k_1 + S}$$



The input-output function can be linearized with a trick:

$$\frac{1}{R_{P\,ss}} = \frac{1}{R_T}\left(1 + \frac{k_2}{k_1}\frac{1}{S}\right)$$



Methods in nonlinear parameter estimation

- Comprehensive grid search: determine the possible range for each parameter, evaluate the model with many combinations of parameters, select the best.
  Improved sampling methods also available

- Iterative parameter search following gradient, steepest-descent or hill-climbing methods
  It is possible to get trapped in local minima/maxima

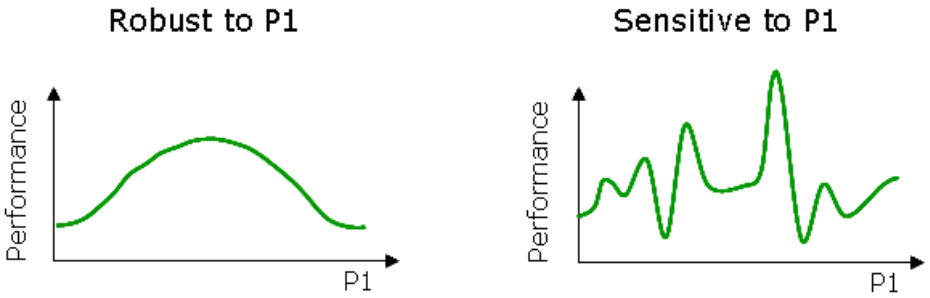
- Genetic algorithm: evolution of a “population” of parameter vectors, “mating” (combination of two vectors), mutations, fitness= match to data
  Relatively slow method, approximate solutions

- In many cases a first evolutionary search is followed by iterative parameter search.

Sensitivity analysis

Systematic investigation of a model's responses to perturbations of variables (node states) or parameters.

- If a system is sensitive to the value of a variable, that variable is a key determinant of the system state.
- If a system is sensitive to the value of a parameter, then either the value of that parameter is tightly regulated, or uncertainties in the value of that parameter will translate into uncertainties in the predicted system behavior.



Methods of sensitivity analysis

- Local methods: variables or parameters are varied one at a time by a small amount around some fixed point and the effect on the output is calculated.

- Global methods: all variables or parameters are varied simultaneously over their entire feasible space, typically using a sampling based approach, and the effects on the output of both individual variables/parameters and interactions between them are assessed.

Local sensitivity analysis

$$\text{Sensitivity} = \frac{\partial(\text{an output measure of interest}) \,/\, (\text{operating point value of the output of interest})}{\partial(\text{an input measure of interest}) \,/\, (\text{operating point value of the input of interest})}$$

First introduced in the context of Metabolic Control Analysis.

It is usually calculated from a Taylor series expansion of the output measure

$$o(t, \boldsymbol{p} + \Delta\boldsymbol{p}) = o(t, \boldsymbol{p}) + \sum_{i=1}^{m} \left. \frac{\partial o(t, \boldsymbol{p})}{\partial p_i} \right|_p \Delta p_i$$

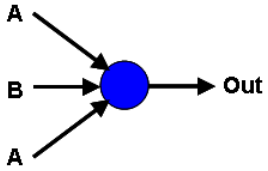
The sensitivity defined this way is a function of time; usually the sensitivity of different operating points is given, or there is an average over sensitivities at different operating points.

Many implementations: SimBiology toolbox of Matlab, BioSens, SensSB.

Metabolic Control Analysis

Goal: to elucidate in quantitative terms to what extent the various reactions of metabolic pathways determine the resulting fluxes and metabolite concentrations.

MCA elasticities measure the sensitivities of transfer functions.



$$\frac{d(out)}{d(t)} = f(A,B,C) - k_d.out$$

$$\text{Elasticity}_{f,A} = \frac{\partial(f)/(\phi)}{\partial(A)/(\alpha)} = \frac{\alpha}{\phi}.\frac{\partial(f)}{\partial(A)}$$

Set point: A=α, f(A,B,C)=Φ

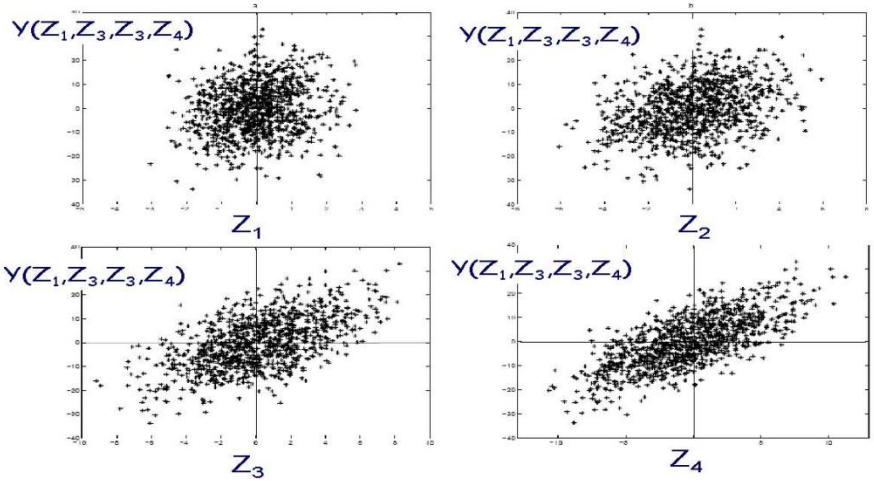
MCA control coefficients measure the response of the system variables after parameter perturbations.

MCA relates node elasticities to the system's control coefficients.

Global sensitivity analysis

- Bifurcation approach: characterize transitions between steady-states that are possible by variations in parameters. Implemented in XPPAUT, Matlab

- Statistical global sensitivity analysis:
  - Assign probability distributions (e.g. uniform, normal) to every parameter
  - Select a sample parameter set (different sampling methods can be used)
  - Estimate the impact of each parameter on the variability of the output (e.g. by keeping a parameter constant and randomly varying the rest)



Implemented in R package “sensitivity”

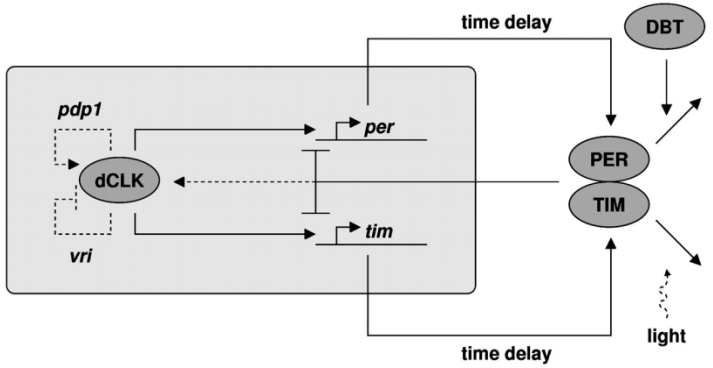
Sensitivity analysis of the circadian clock

Considered two existing models:
single feedback (per only) and double feedback.
Determined the trajectory-integrated local parameter sensitivity of state variables, oscillation period and oscillation amplitude.

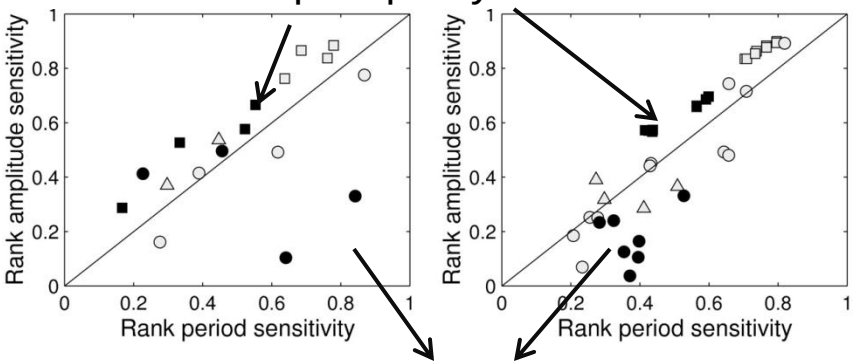
Protein phosphorylation-related parameters mainly influence period, transcription-related parameters mainly influence amplitude.

Parameters can be grouped into global ones - reflecting characteristics of core cellular machineries and local ones - primarily confined to the circadian oscillator.

Higher sensitivity to change in global parameters.



phosphorylation



transcription

Differences in the two models

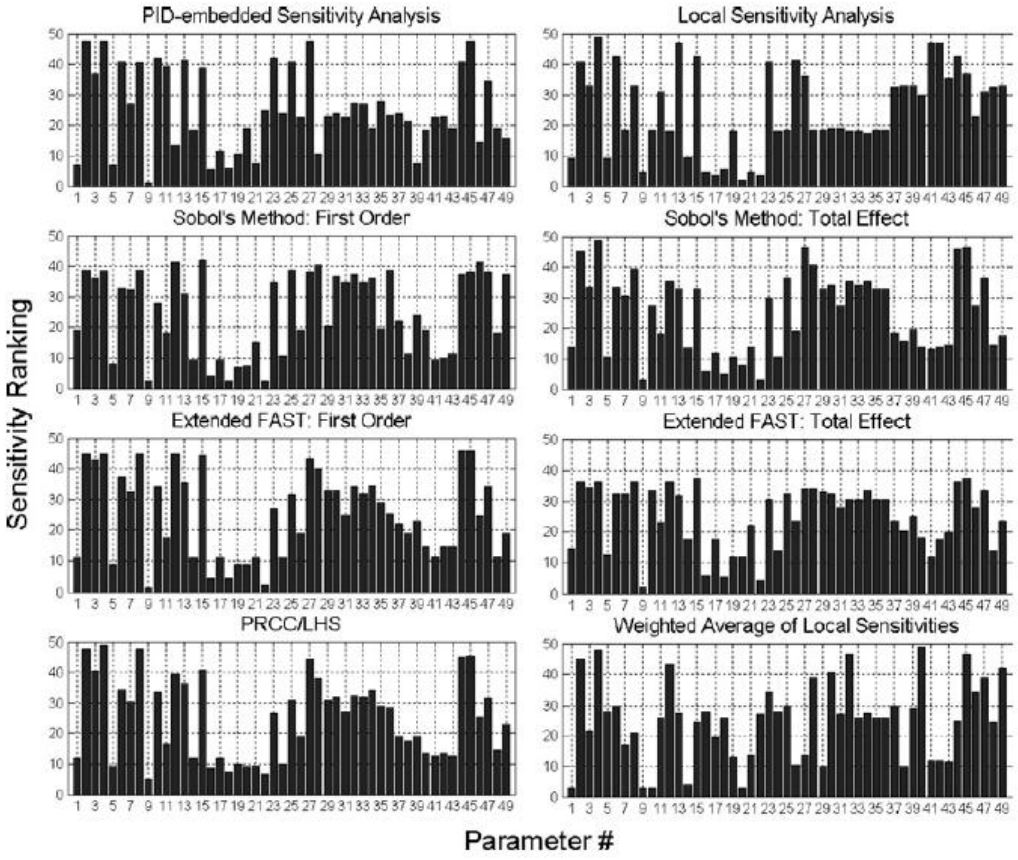
Stelling et al, PNAS 2004.

Comparative sensitivity analysis of Tcr-activated MAPK signaling

ODE model with 24 variables and 69 parameters.
Tried various local and global sensitivity analyses.

Global sensitivity analysis results (Sobol, FAST, PRCC/LHS) consistent with each other.

Identified the most/least sensitive parameters based on global methods



Zheng, Rundel, IEE Proc. Syst. Biol. 2006.